REMARKS

As discussed at the interview, the claims have been amended to require that the animal undergoing whole body external fluorescent optical imaging is mobile and not restrained. Support for this limitation is found on page 8 of the specification, beginning at line 27. Support for the organism being a laboratory animal is found on page 6, at lines 4-5. Support for the clarifying amendment that the fluorophore is a fluorescent protein that is autofluorescent is found on page 9, at lines 11-16. Thus, no new matter has been added and entry of the amendment is respectfully requested.

The ability to image with the animals unrestrained is important for the reasons described in the specification at the noted section. As promised at the interview, sent under separate cover is a short video showing the ability of the claimed method to observe, visually, emitted fluorescence over the whole body in real time. Applicants hope this will be helpful in underscoring the novelty and non-obviousness of their claims.

Claim 37 was rejected under 35 U.S.C. § 102(b) as anticipated by Contag, *et al.* (U.S. 5,650,135). The amendments to the claims clearly distinguish the techniques described by Contag and those in the present application. While Contag mentions fluorescent proteins, which are autofluorescent, as a light-generating moiety, all of the exemplified embodiments in Contag employ luciferase, which is not autofluorescent. This is greatly different in two respects. First, it requires, because of the low intensity of the photon emission, that the subject be immobilized when the imaging takes place. See, for example, claim 1, subparagraph (c). Second, it does not require that there be an excitation beam since it is autofluorescent. Thus, Contag teaches away from the use of fluorescent moieties that are required by the present claims as set forth in column 10, at lines 1-6,

which state that the light used to excite a fluorescent molecule often results in fluorescence of background, especially in a living animal.

The nature of the light emission from luciferase is also as set forth, in subparagraph (d), such that "photon emission" is measured from the light-generating moiety with a photodetector device until an image of photon emission can be constructed. Constructing an image of photon emission is clearly different from simply watching the fluorescent with the naked eye. The method of the present claims permits such observation as shown in the separately mailed video.

There are other reasons that Contag is distinguished as well. As pointed out in the previous response, the only location applicants are able to find in Contag that even mentions monitoring expression controlled by the promoter of an endogenous gene is in column 14, lines 58-65. That paragraph does not recite the steps required in the claim. As the Examiner kindly points out, claim 37 specifically requires (a) administering a test substance to a non-human multicellular organism that expresses a fluorophore under the direction of a promoter of an endogenous gene and (b) determining the expression of the promoter by observing fluorescence generated by the fluorophore at various locations by whole-body external fluorescent optical imaging. There is no mention in the relevant paragraph of administering a test substance to a non-human multicellular organism that expresses a fluorophore under the promoter of an endogenous gene. There is no mention of step (b) of determining the expression of the endogenous promoter in a similar fashion in a control and making the comparison required in step (c) of claim 37. There is no description in that paragraph of a protein that is autofluorescent; there is only mention of luciferase.

Thus, the only place in Contag where monitoring an endogenous gene is described falls far short of detailing the steps that are required in the claimed invention, and does not describe a fluorescent moiety.

The Office cites column 9, at lines 29-42, as teaching that fluorescent proteins can be used as fluorescent moieties, but luciferase is not a fluorescent moiety. Luciferase is, rather, a luminescent moiety that requires substrates to luminesce; it does not require excitation by an external source as does green fluorescent protein. Detecting bioluminescence is an entirely different process from whole-body external fluorescent optical imaging. Such a process is not even implied in the cited paragraph in column 14.

Nowhere in Contag is it said that in all applications of the disclosed methods bioluminescent and fluorescent moieties are interchangeable. Clearly they are not. It cannot be irrelevant, as the Office asserts, that fluorescein is listed in the cited portion of Contag in column 9. The inclusion of molecules such as fluorescein make it clear that that paragraph is not intended to state that all of the listed fluorescent moieties can be used in all embodiments of the described methods. Clearly by listing fluorescein among the fluorescent molecules, the document signals that the fluorescent molecules listed in this paragraph are not necessarily applicable to each embodiment.

In the original basis for rejection, the Office cited column 3, lines 59-61, as showing a comparison between a test subject and a control subject. However, that paragraph, too, is unrelated to the subject matter of the claims. This is said to be useful for monitoring effects of a therapeutic substance administered to a subject on a light-emitting bacterium (*i.e.*, an infectious agent) over time. Clearly the paragraph does not refer to monitoring the expression of an endogenous promoter in response to a test drug. The next section mentioned was column 9, lines 29-32; that has been addressed above. The next section cited in support of the proposition that a nucleic acid comprising

the promoter and fluorophore may be introduced into the animal. Again, this concerns an application that is unrelated to that claimed by the present applicants – apparently this is to test the expression level of a therapeutic gene; the promoter need not be, and presumably is not, an endogenous promoter. Similarly, lines 17-21 of column 4 refer to inducible promoters, presumably non-endogenous ones. The entire discussion in column 4, including lines 6-9, relate to using promoters that are clearly not endogenous and have nothing to do with testing the effect of a test substance on the expression of an endogenous gene.

While the Office is correct that one cannot pick and choose portions of the text from the reference that do not meet the claim limitation, but that the teaching of the entire document should be considered, there appears to be no response to applicants' argument supported by the decision in *Hyatt v. Dudas*, 83 USPQ2d 1373 (Fed. Cir. 2007) that disclosure of separate elements of the invention in unrelated portions of a cited document without showing the connection between these isolated parts cannot be used as a basis for finding anticipation.

While applicants understand that the decision in *Hyatt* was nominally as to whether the examiner had properly made out a *prima facie* case of lack of written description by stating that the elements in the claim were all disclosed individually in the application but that there was nothing which showed the connection between them, the principle remains the same. There is really no description of a combination of elements unless it is described as a combination. Simply taking the listing of fluorescent proteins from one location in Contag in combination with method steps described in entirely different contexts elsewhere is not adequate to teach the combination.

There is nothing in Contag which connects the disclosure in column 14 to the description in column 9, lines 29-42, or to the description in column 3, lines 53-62. Even if these disclosures are

considered together, there is nothing to connect them so as to result in the invention as claimed in claim 37. Accordingly, this basis for rejection should be withdrawn.

Claims 39 and 40 were rejected as assertedly unpatentable over Contag in view of Lin (U.S. 6,380,458). Claim 39 is substantially equivalent to claim 37 except that, rather than looking at the effect on the expression of an endogenous gene of a test substance, the effect of a mutation-inducing agent is determined. The same deficiencies of the Contag disclosure apply here. Lin, too, is deficient. Lin states that "recent chemical mutagenesis screens have generated more than 1,000 different mutants with defects in most developmental processes." Clearly Lin teaches that mutations can be induced in Zebra fish. But that seems to be all. Lin merely states that mutant fish in which the mutant gene is marked with an exogenous construct expressing reporter protein will simplify identification of the fish that carry the mutant gene. However, applicants are unable to find in Lin, even in combination with Contag, any suggestion of the method in claim 39 where an organism is supplied a mutant-inducing agent or treatment when the organism already has an expression system for a fluorophore under the direction of a promoter of an endogenous gene. It appears that Lin merely shows that endogenous promoters linked to green fluorescent protein can be transmitted from generation to generation.

Thus, Lin fails to suggest anything related to the method of claim 39, even when Lin is combined with Contag. In part, this is because Contag does not suggest the basic steps that follow the administration of a mutation-inducing agent or treatment.

Conclusion

In light of the foregoing, it is believed that claims 37 and 39-40 are patentable over the art. Contag fails to disclose or even suggest the steps of subparagraphs a) through c) in either claim 37

or 39, and Lin does not make up for this deficiency with regard to claim 39. Passage of these claims to issue is therefore respectfully requested.

Again, applicants greatly appreciate the time and attention given their undersigned representative in the interview on 15 April.

If minor issues remain that could be resolved by phone, a telephone call to the undersigned would be greatly appreciated.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 312762002710.

Respectfully submitted,

Dated: April 23, 2008

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